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(54) Title: IONTOPHORETIC DELIVERY DEVICES FOR ANTAGONISTS OF GLYCOPROTEIN IIB/IIIA

(57) Abstract

The invention describes an iontophoretic drug delivery device characterised in that it comprises, as an active ingredient, an antagonist of GpIIb/IIIa, and its use in the treatment of a condition which is mediated through the Glycoprotein complex GpIIb/IIIa or other integrin receptor.

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IONTOPHORETIC DELIVERY DEVICES FOR ANTAGONISTS OF GLYCOPROTEIN IIB/IIIA

The present invention relates the iontophoretic delivery to a patient, in particular, to a patient having a thrombotic disorder, of a compound which blocks the binding of fibrinogen to the glycoprotein complex Gp IIb/IIIa. The invention also relates to an iontophoretic delivery device suitable for such use.

Arterial thrombosis, in which platelet activation and aggregation are fundamental processes, makes a major contribution to cardiovascular mortality and morbidity, as evidenced by the incidence of myocardial infarction (1.5 million), unstable angina (1 million) and stroke (550,000) in 1992 in the USA alone. Newer therapies for these thrombotic conditions involve inhibiting platelet aggregation by administering a compound which is capable of blocking the binding of fibrinogen to its platelet receptor, Glycoprotein (Gp)IIb/IIIa. With conventional delivery methods, a problem with this type of therapy which has been realised in the clinic, is that the dramatic anti-platelet effects of such compounds can increase the risk of haemorrhage in patients.

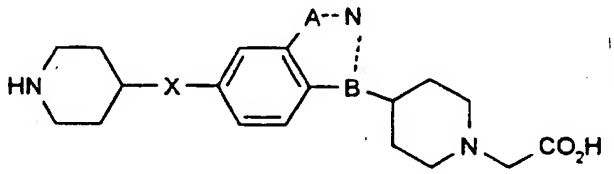
We have now proposed that this problem may be alleviated by administering GpIIb/IIIa antagonists by iontophoretic action. The principle of iontophoresis is that ionised (or polar) drug molecules can be driven across the skin and into the systemic system if an appropriate electrical potential is applied across the skin. This mode of delivery allows such drugs to be administered at a constant and predictable rate so as to keep drug levels within the narrow therapeutic window. Use of iontophoretic delivery is particularly convenient for conditions where the drug is to be administered chronically over a period of several months as it allows for simple self-administration and encourages patient compliance. Furthermore, an iontophoretic delivery system may be removed quickly and easily by the patient or clinician should the need to suddenly stop drug administration arise and normal platelet aggregation would quickly return.

According to the present invention, there is provided an iontophoretic drug delivery device characterised in that it comprises, as an active ingredient, an antagonist of Gp IIb/IIIa. Suitably, said GpIIb/IIIa antagonist is ionised at pH 4 to

7. More suitably, the GpIIb/IIIa antagonist is highly potent, for example requiring a daily dose of less than 50mg/day, and is of low molecular weight.

Examples of GpIIb/IIIa antagonists which may be suitable in the invention include those described in: EP478363B; EP505868B; EP483667A; EP614360B; WO94/22820; Ohman, E.M. et al Eur. Heart J. (1195), 16 (Suppl. L), 50-55; Lincoff, A. et al, Am. J. Cardiol. (1997), 79(3), 286-291; and Timm, U. et al, J. Chromatogr., B: Biomed. Sci. Appl. (1997), 691(2), 397-407, all of which are incorporated herein by reference.

In a preferred aspect of the invention, the GpIIb/IIIa antagonist is of formula (I)



(I)

or a pharmaceutically acceptable derivative thereof, in which:
X is either CH_2-CH_2 or CH=CH; and

either A is  and B is –C=,
or A is –CH= and B is –N–
wherein Y is hydrogen or phenylmethyl wherein the phenyl group is optionally substituted by one or more halogen atoms (where halogen represents fluorine, chlorine, bromine or iodine).

In a further aspect of the invention, the iontophoretic delivery device comprises, as active ingredient, a compound selected from:
{4-[6-(2-piperidin-4-yl-(E)-vinyl)-1H-indazol-3-yl]-piperidin-1-yl}-acetic acid;
{4-[1-(4-fluorobenzyl)-6-(2-piperidin-4-yl-(E)-vinyl)-1H-indazole-3-yl]-piperidin-1-yl}-acetic acid;
{4-[5-(2-piperidin-4-yl-(E)-vinyl)-indazol-1-yl]-piperidin-1-yl}-acetic acid;
{4-[5-(2-piperidin-4-yl-ethyl)-indazol-1-yl]-piperidin-1-yl}-acetic acid,
and pharmaceutically acceptable derivatives thereof.

In a yet further aspect of the invention, the iontophoretic delivery device comprises, as active ingredient, a compound selected from:
{4-[3-methanesulfonyl-5-(2-piperidin-4-yl-ethyl)-indazol-1-yl]-piperidin-1-yl}-acetic acid;
{4-[3-carbamoyl-5-(2-piperidin-4-yl-ethyl)-indazol-1-yl]-piperidin-1-yl}-acetic acid;
{4-[1-methanesulfonyl-6-(2-piperidin-4-yl-ethyl)-1H-indazol-3-yl]-piperidin-1-yl}-acetic acid;
and pharmaceutically acceptable derivatives thereof.

By pharmaceutically acceptable derivative is meant any pharmaceutically acceptable salt, solvate or ester, or salt or solvate of such ester, of the compounds of formula (I), or any other compound which upon adminstration to the recipient is capable of providing (directly or indirectly) a compound of formula (I) or an active metabolite or residue thereof. In a preferred aspect, the GpIIb/IIIa antagonist is in the form of a hydrochloride salt.

In view of their fibrinogen antagonist activity, the iontophoretic drug delivery devices of the present invention are of interest for use in human and veterinary medicine, particularly in the treatment of thrombotic disorders. Particular examples of thrombotic disorders are known in the art and include occlusive vascular diseases such as myocardial infarction, cardiac fatalities, angina, transient ischaemic attacks and thrombotic stroke, arteriosclerosis, vessel wall disease, peripheral vascular disease, nephropathy, retinopathy, postoperative thrombosis, pulmonary embolism, deep vein thrombosis and retinal vein thrombosis. The iontophoretic drug delivery devices of the invention are also of interest for use in the prophylactic treatment of peri- and postoperative complications following organ transplantation (particularly cardiac and renal), coronary artery bypass, peripheral artery bypass, angioplasty, thrombolysis and endarterectomy.

The iontophoretic drug delivery devices of the invention may also be useful for the treatment of other conditions in which the glycoprotein complex Gp IIb/IIIa or other integrin receptors are implicated. Thus, for example, the iontophoretic

drug delivery devices of the invention may potentiate wound healing and be useful in the treatment of bone conditions caused or mediated by increased bone resorption. Particular examples of bone diseases are known in the art and include osteoporosis, hypercalcaemia of malignancy, osteopenia due to bone metastases, periodontal disease, hyperparathyroidism, periarticular erosions in rheumatoid arthritis, Paget's disease, immobilisation-induced osteopenia and glucocorticoid treatment.

The iontophoretic drug delivery devices of the invention may also be useful for the treatment of certain cancerous diseases, for example to prevent or delay metastasis in cancer.

According to a further aspect of the invention, there is provided an iontophoretic drug delivery device characterised in that it comprises, as an active ingredient, an antagonist of GpIIb/IIIa, for use in human or veterinary medicine, particularly for use in the treatment of a condition which is mediated through the Glycoprotein GpIIb/IIIa, for example a thrombotic disorder.

In the alternative, there is provided a method of treating a human or animal subject suffering from a condition which is mediated through the Glycoprotein complex GpIIb/IIIa, for example a thrombotic disorder, which comprises administering an effective amount of GpIIb/IIIa antagonist by iontophoretic action. Preferably, the method comprises administering the GpIIb/IIIa antagonist by an iontophoretic drug delivery device according to the invention.

The process of iontophoretic drug delivery is performed in general by putting the drug, or preferably an iontophoretic delivery device comprising the drug onto intact skin, for example on the arm, chest or the like. The iontophoretic delivery device may contain the drug in isolated form, but more preferably, the drug is in the form of a composition adapted for use in iontophoretic delivery. This composition may for instance be a solution (absorbed onto some porous material, such as a piece of filter paper or a piece of hydrophilic polyurethane) or a gel. The device is then covered by an electrode. A second electrode covering an inert reservoir composed of mainly ionic species is placed elsewhere on the skin, and a direct current source is connected between the electrodes in such a way that the electrode in contact with the drug assumes the

same charge as the ionised drug. Under influence of the electric field present, drug molecules migrate through the skin.

Therefore, according to a further aspect, the invention provides a pharmaceutical composition comprising an antagonist of Gp IIb/IIIa, for example, a compound of formula (I) or a pharmaceutically acceptable derivative thereof, adapted for use in an iontophoretic delivery device.

A useful dose for a human patient, achievable by a device according to the present invention is up to 50 mg/day, preferably up to 25mg/day.

Appropriately, an iontophoretic device according to the present invention substantially as hereinbefore described may be in the form of a matrix of a solid, semi-solid or mucilaginous material having an active ingredient dispersed therein, and optionally having an active ingredient permeable membrane associated therewith. The matrix material is suitably a hydrogel, polyurethane, silicone or other material known in the art for holding a drug in a stable condition prior to release to the skin. Aptly, the matrix is in the form of a transdermal patch or pad, or the like, for transdermal administration of the active ingredient. Alternatively, a device according to the present invention may be in the form of a reservoir having therein a liquid medium containing therein an active ingredient, the reservoir having a membrane which is permeable for the active ingredient. The former option is preferred.

There is further provided by the present invention an iontophoretic drug delivery system which comprises:

(a) an iontophoretic drug delivery device substantially as hereinbefore described; and

(b) electrode means suitable for achieving current flow there between, whereby transdermal administration of an active ingredient to said human or animal subject can be effected.

The electrode means conveniently comprise an electrode system of an anode and a cathode which may be metal foils, polymer matrix loaded with metal powder, powdered graphite, carbon fibres or other suitable electrically conductive material. Suitable metals for use in electrodes are for instance platinum, silver, aluminium, copper, lead, iron, tin, chromium or zinc. Also metal/insoluble salt electrodes may be used, such as silver/silver halide electrodes, particularly silver/silver chloride electrodes. Platinum electrodes are used in some instances, however, silver/silver chloride electrodes are preferred.

The combined skin contacting areas of electrode assemblies can vary from less than $1cm^2$ to greater than $200cm^2$. The average device will have a contacting area from about $5cm^2$ to about $50cm^2$.

A device according to the present invention can be suitably covered by a first electrode. Suitably, a second electrode can be placed elsewhere on the skin, and a direct current source can be connected between the electrodes in such a way that the first electrode in contact with the device containing the active ingredient assumes the same charge as the ionized active ingredient. Under influence of the electric field present, active ingredient molecules migrate through the skin. A current flows between the electrodes, part of which is carried by the active ingredient.

A delivery system according to the present invention may also preferably further comprise a power source, e.g. batteries and suitable control circuitry.

Iontophoretic devices and systems as such are known in the art, for instance from, WO-A 9116946, WO-A 9116944, WO-A 9116943, WO-A 9115261,W0-A 9115260, WO-A 9115259, WO-A 9115258, WO-A 9115257,WO-A 9115250, WO-A 9109645, W0-A 9108795, WO-A 9004433,WO-A 9004432, WO-A 9003825, EP-A 254965, US 4717378, EP-A 252732 and GB-A 2239803.

The present invention will now be illustrated by way of example:

Iontophoretic Transport of {4-[6-(2-piperidin-4-yl-(E)-vinyl)-1H-indazol-3-yl]-piperidin-1-yl}-acetic acid (hereinafter referred to as Test Compound)

The Test Compound and other compounds of formula (I) as defined above may be prepared by methods described in copending applications PCT/EP95/05043 which has the publication number WO96/2012 and GB 9511989.7 which corresponds to PCT application number PCT/EP96/02536. The syntheses of further suitable compounds according to the invention have been described in GB 9613017.4, GB 9613095.0, and GB 9613018.2. The syntheses of all the compounds described above is obvious to a person skilled in the art of chemistry.

1. Method of Quantification

High performance liquid chromatography (HPLC) was used to determine the concentration of Test Compound in solution. The mobile phase consisted of 70:30 0.05% trifluoroacetic acid (TFA) in purified water: 0.05% TFA in acetonitrile. All solvents were HPLC grade. The λ_{max} was determined to be 237nm by scanning techniques and was used for the wavelength of detection in this assay. Flow rate was maintained at 1.5mL/min. A 15 x 0.46 cm Spherisorb phenyl column, 3µm packing was used.

2. Iontophoresis Method

Two sets of experiments were conducted using a Scepter iontophoretic system controller by Keltronic Corporation. The system consists of a PC, 6 sets of electrode leads, and 2 temperature leads. All currents used were DC. Current densities were held at 0.1mA/cm^2 of skin or membrane (0.678cm^2) equivalent to a current setting of 0.07mA. Currents were monitored over the time course of the experiment and were held within ±0.01mA. Voltages and currents were checked independently using a hand-held voltmeter.

Electrodes were fabricated in the lab from silver wire (99.9985% pure, 0.5mm in diameter, Alfa Aesar Puratronic, Johnson Matthey). Preparation involved placing two equal lengths of silver wire in 0.5M KCl and applying a current of 1mA for 12 hours. This process is taken from the procedure demonstrated by Burnette and Ongpipattanakul, (1988), Journal of Pharmaceutical Sciences,

77(2), 132-7. The Ag:AgCl electrodes produced were coiled around a 22G 1.5inch syringe needle to produce a coil approximately 1.125inches in length and a lead of approximately 1.25inches. The total area of the electrode was 3.39cm^2. The anode (+) electrode (Ag) was placed in the donor solution in order to repel the positively charged drug substance across the membrane. The cathode (-) electrode (AgCl) was placed in the receptor side of the diffusion cell. The electrodes were located approximately 3cm apart.

Cell cultures utilized were produced from healthy human keratinocytes and were obtained from MatTek Corporation (EpiDerm EPI-606) and used upon receipt. Cultures were carefully removed from their support, rinsed with 0.1M NaCl (receptor solution), and placed in the diffusion cells with the top exposed portion of the culture ("stratum corneum") facing the donor side of the cell set-up. Human cadaver skin was obtained from the International Institute for the Advancement of Medicine (IIAM). Skin samples were cut into 2.5 x 2.5 cm squares and rinsed with water for injection containing 60µg/mL gentamicin before being placed in the diffusion cells (stratum corneum facing the donor compartment). Skin samples used in this study were from the thigh region and were dermatomed by IIAM before shipment.

Six sets of Crown Glass side-by-side diffusion cells with magnetic stirrers were employed in each experiment. Four cells were run under iontophoretic conditions and two cells were run under passive conditions. A temperature of 32°C was maintained throughout the duration of the experiment by using a recirculating water bath. Temperature was monitored throughout the experiment by the Scepter system temperature probes. Experiments were conducted for 5 hours with the cell cultures and 8 hours with the skin samples. Additionally, 20 hours of passive data was collected for experiments using human cadaver skin. pH of the initial and final donor solution and sampled receptor solutions were measured using a Corning Ion Analyzer 255 pH meter and recorded. All solutions were protected from light throughout the time course of the experiment.

The donor solution consisted of an 8.5mg Test Compound/ml aqueous solution, pH 5, unadjusted. The receptor solution consisted of 0.1M NaCl aqueous

solution adjusted to pH 5 with NaOH/HCl. The volume of the donor and receptor compartments were 3.5mL and the receptor compartment was emptied at each sample interval and filled with 3.5mL of fresh, pre-heated receptor solution. A mass balance was performed at the completion of each run.

3. Data Treatment

Standard area counts were entered into a spreadsheet and a linear regression analysis was performed on the average area counts *versus* concentration (µg Test Compound/mL). Content data for the samples were generated from area counts using the standard regression curve. The amount of Test Compound transported for each sample was calculated based on 3.5mL receptor solution volume. Cumulative amounts, instantaneous fluxes, and cumulative amounts per cm^2 of skin or culture were subsequently determined from these values.

Steady state flux values were determined from cumulative µg Test Compound/cm^2 *versus* time (hr) plots of the data. Regression analysis conducted on the steady state portion of these profiles provided flux data from the slope and lag time data from the x-intercept. The predicted anode area was determined by dividing the desired delivery rate (750µg Test Compound/hr) by the flux (µg Test Compound/cm^2 hr). The predicted patch size was calculated by multiplying the anode area by 2.5 (anode + cathode + additional housing area) as recommended Sage Jr. & Riviere, (1992). "Model systems in iontophoresis-transport efficacy" Advanced Drug Delivery Reviews, 9, 265-287. Flux data was scaled linearly in order to predict the flux, anode area, and system size at other current densities.

Plasma levels were predicted based on the relationship:

$$C_p = \frac{J \cdot A_{anod}}{Cl}$$

where C_p is the predicted plasma level (ng/mL), J is the steady-state flux (µg/cm^2hr), A_{anode} is the area of the anode (cm^2), and Cl is the clearance (mL/min).

Human Keratinocyte Cell Cultures

The results obtained from this set of experiments are listed in Tables 1 and 2 as µg Test Compound/cm^2 of culture available for transport. Active cells were run at a current density of 0.1mA/cm^2. System suitability standard checks were run five times throughout the analysis and results were found to be between 97.7 and 98.7% of the actual concentration based on regression analysis. A mass balance conducted at the conclusion of this experiment demonstrated at least 100% recovery from each diffusion cell set-up. All results are corrected for purity and reported in terms of the free base of the Test Compound.

Table 1: Average Cumulative µg Test Compound/cm^2 Transported
- Active Transport Cultures -

Time (hr)	Mean (µg/sq cm) (n=4)	Standard Deviation	Coeff. of Var. (%)	±95% conf.int.
0.50	0.00	n/a	n/a	n/a
1.0	0.00	n/a	n/a	n/a
3.0	33.93	12.45	36.69	19.81
5.0	72.36	15.67	21.66	24.94

Table 2: Average Cumulative µg Test Compound/cm^2 Transported
- Passive Transport Cultures -

Time (hr)	Mean (µg/sq cm) (n=2)	Standard Deviation	Coeff. of Var. (%)	±95% conf. int.
0.50	0.00	0.00	n/a	n/a
1.0	0.00	0.00	n/a	n/a
3.0	0.00	0.00	n/a	n/a
5.0	0.00	0.00	n/a	n/a

Human Cadaver Skin

The results obtained from this set of experiments are listed in Tables 3 and 4 as µg Test Compound/cm^2 of skin available for transport. Active cells were run at a current density of 0.1mA/cm^2. System suitability standard checks were run seven times throughout the analysis and results were found to be between 93.5 and 94.6% of the actual concentration based on regression analysis. A mass balance conducted at the conclusion of this experiment demonstrated at least 100% recovery from each diffusion cell set-up. All results are corrected for purity and reported in terms of the free base of the Test Compound.

Table 3: Average Cumulative µg Test Compound/cm^2 Transported - Active Transport Skin -

Time (hr)	Mean (µg/sq cm) (n=4)	Standard Deviation	Coeff. of Var. (%)	±95% conf. int.
1.00	49.14	37.65	76.63	59.91
2.00	127.40	77.87	61.12	123.91
3.00	216.05	108.39	50.17	172.48
5.00	408.19	192.52	47.17	306.36
6.00	522.48	226.80	43.41	360.90
8.00	738.53	311.94	42.24	496.37

Table 4: Average Cumulative µg Test Compound/cm^2 Transported - Passive Transport Skin -

Time (hr)	Mean (µg/sq cm) (n=2)	Standard Deviation	Coeff. of Var. (%)	±95% conf. int.
1.00	4.33	1.57	36.23	14.10
2.00	8.98	3.73	41.57	33.54
3.00	12.91	5.65	43.76	50.78
5.00	20.04	10.78	53.81	96.88
6.00	24.34	13.88	57.04	124.73
20.00	89.69	53.94	60.14	484.65

Iontophoretic Feasibility Assessment

Based on the fluxes obtained and reported lag times, extrapolated fluxes at various current densities, and predicted patch surface area can be calculated. These results are shown in Table 5. Also, by taking into account the estimated clearance value for this compound (250 mL/min), we can calculate the predicted plasma concentrations. These predictions are also shown in Table 5.

Table 5: Test Compound Iontophoretic Transport Feasibility Results

	Human Cadaver Tissue (thigh)	Human Cell Cultures (keratinocytes)
Steady-state flux* ($\mu g/cm^2 hr$)	102±8 (n=4)	19±1 (n=4)
Lag time to reach steady-state (hr)	0.7	0.9
Patch size required for 750µg delivery in 1hr (cm^2)@		
$0.05 mA/cm^2$	37	200
$0.1 mA/cm^2$	18	99
$0.3 mA/cm^2$	6	33
$0.5 mA/cm^2$	4	20
Predicted plasma levels†	49ng/mL	50ng/mL

* calculated from cumulative amount/cm^2 *versus* time plots, based on surface area of skin available for transport

@ patch total area calculated is approximately 2.5×(anode area) since cathode and system housing is required for complete device; based on steady-state flux values

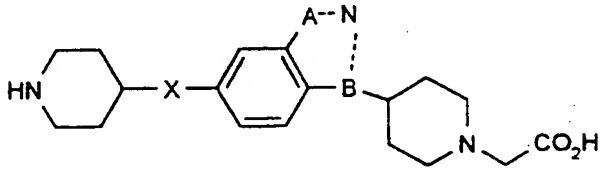
† Clearance = 250mL/min.

The results obtained indicate that therapeutic plasma levels of Test Compound can be obtained by iontophoretic delivery of its hydrochloride salt.

CLAIMS

1. An iontophoretic drug delivery device characterised in that it comprises, as an active ingredient, an antagonist of Gp IIb/IIIa.

2. An iontophoretic drug delivery device according to claim 1 wherein the GpIIb/IIIa antagonist is of formula (I)



(I)

or a pharmaceutically acceptable derivative thereof, in which:
X is either CH_2-CH_2 or CH=CH; and

either A is $-\overset{Y}{\underset{|}{N}}-$ and B is –C=,
or A is –CH= and B is –N–
wherein Y is hydrogen or phenylmethyl wherein the phenyl group is optionally substituted by one or more halogen atoms.

3. An iontophoretic delivery device according to claim 1 or 2 wherein the Gp IIb/IIIa antagonist is selected from:
{4-[6-(2-piperidin-4-yl-(E)-vinyl)-1H-indazol-3-yl]-piperidin-1-yl}-acetic acid;
{4-[1-(4-fluorobenzyl)-6-(2-piperidin-4-yl-(E)-vinyl)-1H-indazole-3-yl]-piperidin-1-yl}-acetic acid;
{4-[5-(2-piperidin-4-yl-(E)-vinyl)-indazol-1-yl]-piperidin-1-yl}-acetic acid;
{4-[5-(2-piperidin-4-yl-ethyl)-indazol-1-yl]-piperidin-1-yl}-acetic acid;
{4-[3-methanesulfonyl-5-(2-piperidin-4-yl-ethyl)-indazol-1-yl]-piperidin-1-yl}-acetic acid;
{4-[3-carbamoyl-5-(2-piperidin-4-yl-ethyl)-indazol-1-yl]-piperidin-1-yl}-acetic acid;
{4-[1-methanesulfonyl-6-(2-piperidin-4-yl-ethyl)-1H-indazol-3-yl]-piperidin-1-yl}-acetic acid;

and pharmaceutically acceptable derivatives thereof.

4. An iontophoretic drug delivery device as defined in any one of Claims 1 to 3 for use in human or veterinary medicine.

5. An iontophoretic drug delivery device as defined in any one of Claims 1 to 3 for use in the treatment of a condition which is mediated through the Glycoprotein complex GpIIb/IIIa or other integrin receptor.

6. A method of treating a human or animal subject suffering from a condition which is mediated through the Glycoprotein complex GpIIb/IIIa receptor, which comprises administering a GpIIb/IIIa antagonist by an iontophoretic drug delivery device according to any one of claims 1 to 3.

7. A pharmaceutical composition comprising an antagonist of Gp IIb/IIIa or a pharmaceutically acceptable derivative thereof, adapted for use in an iontophoretic delivery device.

INTERNATIONAL SEARCH REPORT

Inte onal Application No
PCT/GB 97/01670

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K9/00 A61K31/415 A61K31/445

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 458 568 A (RACCHINI JOEL R ET AL) 17 October 1995 see column 6, line 32 - line 33 see column 10, line 29 - column 11, line 31 ---	1,7
X	US 5 510 328 A (POLAREK JAMES ET AL) 23 April 1996 see column 8, line 18 - line 20 see column 4, line 42 - line 52 ---	1,7
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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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18 September 1997	02. 10. 97
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+ 31-70) 340-3016	**Authorized officer** Foerster, W

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